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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/445,223	12/06/1999	DAVID WALLACH	WALLACH=24	9660

1444 7590 12/02/2004

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 12/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/445,223	WALLACH ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05/11/04, 05/14/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-8, 11, 22-24, 29-30, 40-48, 51-* is/are pending in the application.

4a) Of the above claim(s) *22,29,30 and 40-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-8,11,23,24,44-48 and 51-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The finality of the previous Office action has been withdrawn, and the prosecution of this application is reopened to include art not previously cited.

It is noted that applicant has paid for a Notice of Appeal. Applicant can either request a refund or place the funds on credit for future appeals.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 5-8, 11, 23-24, 44-48, 51-54 are being examined.

The following are the remaining rejections.

SPECIFICATION

1. The substitute specification submitted on 02/28/02 lacks references 53-75 cited in the original specification.

2. The amendment of 05/11/04 of the substitute specification on page 61, line 1, is acknowledged.

SEQUENCE RULE COMPLIANCE

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. 1.821-25 for the following reasons:

The cited sequences in the specification are not accompanied by sequence identification numbers. For example, Figure 3 legend on page 18 and the sequence cited on page 38 lack sequence identification numbers.

REJECTION UNDER 35 USC 101, NEW REJECTION

35 U.S.C. §101 states:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 51, 53 are rejected under 35 USC 101 because the claimed invention is directed to non-statutory subject matter.

Claims 51, 53, as written, do not sufficiently distinguish over oligonucleotides, as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified". See MPEP 2105.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE, NEW REJECTION

Claims 8, 11 are rejected under 112, first paragraph, because the specification, while being enabling for an isolated, transformed eukaryotic host cell containing a vector according to claim 5, **is not reasonably enabled for transformed eukaryotic host cell containing a vector according to claim 5**.

Claims 8, 11 are drawn to transformed eukaryotic host cells containing a vector according to claim 5, and a method for producing a polypeptide that potentiates cell death, using said transformed host cells.

The specification contemplates the use of recombinant animal virus such as Vaccinia containing the claimed polynucleotide for introducing in vivo into target cells, such as tumor or HIV infected cells for treating cancer of AIDs (p.31, third paragraph).

The claims encompass an in vivo host cell from gene therapy, and a method of producing a polypeptide that potentiates cell death, comprising growing said host cell.

One cannot extrapolate the teaching in the specification to the scope of the claims. The state of the art at the time of filing was that the combination of vector, promoter, protein, cell, target tissue, level of expression and route of administration required to target the tissue of interest and obtain a therapeutic effect using gene therapy was unpredictable. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1).

Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

In view of the unpredictability of gene therapy, and the lack of disclosure of how to successfully produce in vivo host cell that express the claimed sequence, it would be undue experimentation for one of skill in the art to practice the claimed invention

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

If Applicant could overcome the above 112, first paragraph, rejection under 35 USC 112, first paragraph of claims 5-8, 11, 23-24, 44-48, 51-52, pertaining to lack of enablement for a DNA sequence encoding a polypeptide analog or fragment of SEQ ID NO:1, which analog or fragment potentiates cell death, still remains for reasons already of record in paper of 01/15/04.

Applicant argues that the Examiner did not response to each of the six points in the response of 10/07/04.

Applicant further argues that while protein chemistry is somewhat unpredictable, this certainly would not be expected for every amino acid, and that the basic expectation would be that small changes would not dramatically affect the biological activity.

Applicant further argues that the biological activity could be readily tested, and the Examiner has not explained why it would take undue experimentation to test any given proposed mutein having no more than 10 changes in amino acid sequence.

Applicant's arguments set forth in paper of 05/11/04 and 05/14/04 have been considered but are not deemed to be persuasive for the following reasons:

Although the Examiner's response was not laid out as 1-6 points, the rejection clearly addressed all 6 points cited by Applicant. The Examiner reiterates the rejection as follows:

1) Concerning Applicant's argument that changes are of less than 2%, and that the Office has conceded that a single example is representative of the entire genus of variants with 95% identity, and thus the claimed analog does not have a particularly wide breadth, this is not found to be persuasive.

The Examiner has clearly stated and reiterates here that protein chemistry is unpredictable, and that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristics of a protein, as taught by Burgess et al, Lazar et al, Tao et al, and Gillies et al, all of record. The specification however does not teach how to make the claimed analogs or fragments such that they function as claimed. The specification does not teach which amino acids are essential for potentiating cell death. The specification does not teach which amino acids could be substituted, added or deleted such that the claimed analogs or fragments still could potentiate cell death. The specification does not teach which amino acids could be added to or used for the contemplated substitution of the original amino acids, such that the claimed analogs or fragments still could potentiate cell death. Thus in view of such unpredictability, and with inadequate teaching in the specification, one would not know how to make the claimed analogs or fragments. Further, with such unpredictability it would be undue experimentation for one of skill in the art to screen for the claimed analogs or fragments.

Moreover, Applicant clearly misinterpretes the Examiner when reciting that the Office has conceded that a single example is representative of the entire genus of variants with 95% identity. The Examiner did not state that a single example is representative of the entire genus of variants with 95% identity. One the contrary, from a single example of the polynucleotide of SEQ ID NO:2, one would not know how to make or screen for the claimed analogs of fragments such that they would potentiate cell death, in view of the unpredictability of protein chemistry, supra. This rejection is clearly

supported by MPEP 2164.08(a), which teaches that a single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claims because the specification disclosed at most only those means known to the inventor. *In re Hyatt*, 708 F.2d 712, 714-715, 218 USPQ 195, 197 (Fed. Cir. 1983). In the instant application, the specification only discloses the polynucleotide of SEQ ID NO:2, the scope of the claims however encompasses numerous analogs or fragments of SEQ ID NO:2 that potentiate cell death, with unknown structure. The specification however does not teach which amino acids are essential for potentiating cell death. The specification does not teach which amino acids could be changed such that the claimed analogs or fragments still could potentiate cell death. The specification does not teach which amino acids could be added to or used for the contemplated substitution of the original amino acids, such that the claimed analogs or fragments still could potentiate cell death. Thus the claims would be non-enabled according to MPEP 2164.08(a).

2) Concerning the arguments that the nature of the invention is such that substantial experimentation is reasonably conducted by one of skill in the art, Applicant must not be limited to exemplified embodiments, and that as long as it is shown the experimentation to determined what falls within the claims is not undue, the enablement requirement is met, this argument is found not to be persuasive.

The Examiner has recited MPEP 2164.03, which teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher,

427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

The specification however does not teach how to make the claimed analogs or fragments such that they function as claimed. The specification does not teach which amino acids are essential for potentiating cell death. The specification does not teach which amino acids could be changed such that the claimed analogs or fragments still could potentiate cell death. The specification does not teach which amino acids could be added to or used for the contemplated substitution of the original amino acids, such that the claimed analogs or fragments still could potentiate cell death.

Thus in view of the teaching of MPEP 2164.03, it is clear that given the unpredictability of protein chemistry, the specification's lack of adequate disclosure in the specification of how to make the claimed analogs or fragments such that they would function as claimed, and in view of the complex nature of the claimed invention, and since little is known in the art about the claimed invention, the specification would need more detail as how to make and use the invention in order to be enabling. Thus one of

skill in the art would be forced into undue experimentation to practice the claimed invention.

3) Concerning Applicant's argument that as to the level of one of skill in the art, because of the extremely high level of ordinary skill, even complex experimentation is not necessarily undue, as stated in previous Office action, and supra, although complex experimentation is not necessarily undue, given the unpredictability of protein chemistry, supra, the lack of adequate disclosure in the specification of how to make the claimed analogs, or fragments such that they would function as claimed, supra, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention

4) Concerning Applicant's argument that as to the predictability in the art, when changing the sequence by less than 2% , there would be an expectation that the function is maintained, this is not found to be persuasive.

It is noted that **Applicant's position that "when changing the sequence by less than 2%, there would be an expectation that the function is maintained" is not supported by any references or any teaching in the art.**

The Examiner clearly has stated that the level of unpredictability is very high in the instant application because the protein art is unpredictable, as taught by Burgess et al, Lazar et al, Tao et al, and Gillies et al, all of record, supra, and one cannot predict which of the numerous analogs or fragments of SEQ ID NO:2 potentiate cell death. Further, one would not know how to make the claimed analogs or fragments such that

they would potentiate cell death in view of such unpredictability. Further, with such unpredictability, it would be undue experimentation for one of skill in the art to screen for the claimed analogs or fragments.

5) Concerning guidance by the specification, such as screening assays, and preferred substitution, the Examiner has clearly stated that the guidance is inadequate, in view of the teaching of MPEP 2164.03, supra, and in view of the unpredictability of protein chemistry, supra. The specification does not teach which amino acids are essential for potentiating cell death. The specification does not teach which amino acids could be added or deleted or substituted such that the claimed analogs or fragments still could potentiate cell death. The specification does not teach which amino acids could be added to or used for the contemplated substitution of the original amino acids, such that the claimed analogs or fragments still could potentiate cell death.

In view of the unpredictability of protein chemistry, supra, and in view of inadequate teaching in the specification, one would not know how to make the claimed analogs or fragments such that they would potentiate cell death. Further, although screening assay is known in the art and taught in the specification, however, with such unpredictability, it would be undue experimentation for one of skill in the art to screen for the claimed analogs or fragments.

6) Concerning working examples, such as cell death assays, the examples provided in the specification are not adequate. The specification does not teach how to make the claimed analogs or fragments such that they still potentiate cell death. With such unpredictability of protein chemistry, as taught by Burgess et al, Lazar et al, Tao et al,

and Gillies et al, all of record, it would be undue experimentation for one of skill in the art to screen for the claimed analogs or fragments using the death assays. As taught by MPEP 2164.03, supra, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Thus it would be undue experimentation for one of skill in the art to make and use the claimed analogs or fragments given limited disclosure in the specification, such as only a single example of the polynucleotide of SEQ ID NO:2, and the cell death assays, and given the unpredictability of protein chemistry, supra.

Concerning the quantity of experimentation, and Applicant's arguments that a considerable amount of experimentation is permissible, and that the procedure, such as mutagenesis and cell death assays, is routine in the art, this is not found to be persuasive.

Although the procedure, such as mutagenesis and cell death assays, is routine in the art, however, view of such unpredictability of protein chemistry, supra, and in view of inadequate teaching in the specification of which amino acids to mutagenize or delete or substitute or added such that the claimed analogs or fragments still potentiate cell death, one would not know how to make the claimed analogs or fragments such that they would potentiate cell death, and it would be undue experimentation for one of skill in the art to screen for the claimed analogs or fragments.

Thus the breadth of the claims is overly broad, encompassing numerous analogs and fragments of the polynucleotide of SEQ ID NO:2 that potentiate cell death, with

unknown structure, and it would be undue experimentation for one of skill in the art to practice the claimed invention.

REJECTION UNDER 35 USC 102 (e), NEW REJECTION

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 24, 51 are rejected under 35 U.S.C. 102(e) as being anticipated by US 5,578,468.

Claims 24, 51 are drawn to an oligonucleotide molecule or a composition comprising a pharmaceutically acceptable excipient and an oligonucleotide molecule

consisting of an antisense sequence of at least a part of an mRNA sequence corresponding to a DNA sequence of claim 44, which is an isolated DNA sequence encoding a polypeptide which potentiates cell death, said polypeptide consisting of:

a) a sequence comprising SEQ ID NO:1;

b) a sequence comprising an analog of (a) having no more than ten changes in the amino acid sequence of (a), each of said change being a substitution, deletion or insertion of a single amino acid, which analog potentiates cell death, or

c) a fragment of the sequence of SEQ ID NO:1, which fragment potentiates cell death.

It is noted that since there is no definition of "corresponding" in the specification, any mRNA sequence would "correspond" to a DNA sequence of claim 44.

It is further noted that due to the language "at least a part of", claim 51 encompasses an antisense sequence of any length to any part of a mRNA corresponding to a DNA sequence of claim 44.

In addition, it is noted that SEQ ID NO:2 encodes SEQ ID NO:1 of claim 44.

US 5,578468 teaches a sequence having site-specific RNA cleavage, consisting of 37 nucleotides (SEQ ID NO:44). Under MPSRCH sequence similarity search, SEQ ID NO:44 is 100% similar to SEQ ID NO:2 of the claimed invention, which encodes SEQ ID NO:1, from nucleotide 2067 to nucleotide 2098 (MPSRCH search report, 2004, us-09-445-223-2.olig-11.rni, pages 1-2). US 5,578,468 also teaches that these sequences having site-specific RNA cleavage could be produced in vitro by incubation RNAs in a

reaction mixtures containing buffer supplemented with extract of Hela cells infected with vaccinia virus (figure 2 legend on column 3).

It is noted that it is well known in the art that buffer is a pharmaceutically acceptable excipient, because buffer has been commonly used in assays for in vitro screening or testing, such as the assay taught by US 5,578,468.

Given the sequence taught by US 5,578,468, one would readily envision the claimed antisense molecule and a composition comprising a pharmaceutically acceptable excipient and said antisense molecule.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

October 26, 2004